Cause-Specific Late Mortality Among 5-Year Survivors of Childhood Cancer: The Childhood Cancer Survivor Study

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Background The proportion of pediatric and adolescent cancer patients surviving 5 years has increased during the past four decades. This growing population of survivors remains at risk for disease- and treatment-associated late mortality.

Methods A total of 20483 five-year survivors of childhood and adolescent cancer diagnosed between January 1, 1970, and December 31, 1986, and enrolled in the Childhood Cancer Survivor Study (CCSS) were included in a National Death Index search for deaths occurring between January 1, 1979, and December 31, 2002. Treatment information was abstracted from primary medical records. Survival probabilities, standardized mortality ratios (SMRs), and absolute excess risks were calculated for overall and cause-specific deaths. Diagnosis- and sex-specific survival probabilities were estimated by the product-limit method. All statistical tests were two-sided.

Results Among the CCSS cohort, 2821 (13.8%) 5-year survivors had died by the end of the follow-up period. The cause of death was obtained for 2534 individuals, with 57.5% of deaths attributed to recurrent disease. Estimated probability of survival 30 years from diagnosis was 82%. When compared with the US population, the absolute excess risk of death from any cause was 7.36 deaths per 1000 person-years. The overall SMR was 8.4 (95% confidence interval [CI] = 8.0 to 8.7). Increases in cause-specific mortality were seen for deaths due to subsequent malignancy (SMR = 15.2, 95% CI = 13.9 to 16.6) and cardiac (SMR = 7.0, 95% CI = 5.9 to 8.2), pulmonary (SMR = 8.8, 95% CI = 6.8 to 11.2), and other medical (SMR = 2.6, 95% CI = 2.3 to 3.0) causes. At 20 years of follow-up (25 years after first cancer diagnosis), the death rate due to a subsequent malignancy exceeded that due to all other causes.

Conclusion Our extended follow-up of 5-year survivors of pediatric and adolescent cancer indicates that excess mortality persists long after diagnosis. Continued observation is needed to further define lifetime risk and to determine the potential contribution of chronic health conditions and modifiable health behaviors.

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Advances in cancer therapy during the past four decades have resulted in remarkable increases in survival for most cancers of childhood and adolescence. Population-based statistics show the probability of 5-year survival of cancer in those under the age of 20 in the United States to be 80% (1). As a result, more than 7000 individuals are expected to join the more than 300000 five-year survivors of childhood cancer in the United States in the next year. These long-term survivors are at risk for life-threatening late effects of their childhood cancer including second malignancies, cardiac and vascular abnormalities, and pulmonary complications (2–7). Previous studies of childhood cancer survivors (8–16) have shown excesses in long-term mortality and have defined high-risk groups by demographic and treatment characteristics.

The Childhood Cancer Survivor Study (CCSS) is a retrospectively assembled cohort with subsequent prospective follow-up. At the time the CCSS cohort was constructed, we reported on subsequent mortality ascertained as of December 31, 1996, among the 5-year survivors (13). We now report results of an expanded analysis of mortality based on more than 130000 additional person-years of observation, during which 800 additional deaths occurred. Our objective was not only to describe temporal patterns in cause-specific mortality but also to investigate factors predictive of increased risk for late mortality.

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Subjects and Methods

Study Population

The CCSS is a multi-institutional study (see Appendix 1) of individuals who survived for 5 or more years after treatment of cancer diagnosed during childhood or adolescence. Eligibility criteria for CCSS are as follows: 1) diagnosis of leukemia, central nervous system (CNS) malignancies (all histologies), Hodgkin disease, non-Hodgkin lymphoma, malignant kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; 2) diagnosis and initial treatment at one of the 26 collaborating CCSS institutions; 3) diagnosis between January 1, 1970, and December 31, 1986; 4) age at diagnosis less than 21 years; and 5) survival 5 years from the date of diagnosis. Details of the study design, methods, and cohort characteristics have been reported previously (17). The CCSS protocol and contact documents were reviewed and approved by the Human Subjects Committee at each participating institution. Written informed consent was received from all participating subjects 18 years of age or older and from a parent or guardian for subjects under the age of 18.

Cancer Treatment Information

Characteristics of the original cancer diagnosis were obtained from the treating institution for all eligible cases. Detailed treatment information, including that pertaining to chemotherapy, radiation therapy, and surgery, was abstracted from the primary medical records. The medical record abstraction form used in data collection is available at www.stjude.org/ccss.

For purposes of analysis, similar chemotherapeutic agents were grouped together. Patient-specific alkylating agent scores were calculated, summing the tertiles of each drug received (18). Anthracycline exposure (per square meter) consisted of the sum of the doxorubicin and daunorubicin doses and three times the idarubicin dose (19). Cumulative exposure to epipodophyllotoxins (per square meter) was the sum of teniposide (VM-26) and etoposide (VP-16). In the analysis of overall mortality and death due to a subsequent malignancy, assessment of radiation-associated risk used a dichotomous yes/no variable for indicating the exposure to radiotherapy; for cardiac-related deaths, exposure (yes/no) to radiotherapy involving the chest or spine was considered; and for pulmonary complications, exposure of the chest area to radiotherapy was used.

Causes of Death

Methods for ascertaining and categorizing deaths within the CCSS cohort have been described previously (13). In brief, individuals eligible for the CCSS cohort whose vital status as of December 31, 2002, was unknown and those who were reported to have died after cohort entry were included in a National Death Index (NDI) search for deaths that occurred between January 1, 1979, and December 31, 2002. For those who died in the United States, cause of death information was provided by the NDI, using the International Classification of Diseases, Ninth Revision (ICD-9), classification (20). For deaths that occurred in 1975 through 1978 (ie, the years not covered by the NDI), copies of the death certificates were requested from all states where such deaths occurred. Death certificate data were not available for individuals who were Canadian residents at the time of death; therefore, these individuals were excluded from the cause-specific morality analysis, although they were included in all other analyses.

CONTEXT AND CAVEATS

Prior knowledge

The number of survivors of pediatric and adolescent cancers has greatly increased. The additional risks of mortality that these individuals face due to their childhood cancer and its treatment need to be quantified.

Study design

Deaths of 5-year survivors of childhood cancer in the Childhood Cancer Survivor Study were obtained from the National Death Index, and treatment information was from medical records. Standard mortality ratios and absolute excess risks were determined, and diagnosis- and sex-specific survival probabilities were calculated by the product-limit method.

Contribution

With extended follow-up of the largest cohort of 5-year survivors of childhood and adolescent cancer that has been studied, the authors quantified the temporal trends in the increases in mortality that are due to second malignancy, cardiac disease, pulmonary disease, and other causes. The increases were found to persist long after diagnosis, and this study identified some of the factors (eg, type of original cancer, type of treatment) associated with higher mortality in the survivors.

Implications

Continued observation of this and similar cohorts is needed to further define lifetime risks of mortality in 5-year survivors and its associations with chronic health conditions and modifiable behaviors.

Limitations

The reliance on death certificate information may have entailed some inaccuracy in estimates of mortality due to specific causes.

From the Editors

Statistical Analysis

Follow-up for this study began on the date 5 years after the original cancer diagnosis and ended on either the date of death or the date of censoring (December 31, 2002). Standardized mortality ratios (SMRs) for 5-year age groups were calculated using the expected number of deaths based on age-, year-, and sex-specific US mortality rates and the corresponding person-years at risk observed (21).

Causes of death were grouped into six categories—recurrence and/or progression of disease, secondary or subsequent cancer (ICD 140–239), cardiac (ICD 390–398, 402, 404, 410–429), pulmonary (ICD 460–519), external causes (accidents, suicide, poisoning, etc; ICD 800–999), and other causes (all other ICD codes). Only deaths with known causes and not due to recurrence of the original cancer were included in the calculation of cause-specific SMRs.

Diagnosis- and sex-specific survival probabilities were estimated by the product-limit method (22), as well as for groups conditioned on their survival of 10, 15, and 20 years to obtain conditional survival probability estimates. To compare survival for the CCSS cohort with the age-comparable US population, an expected number of deaths for each year since diagnosis was calculated based on the US age-, year-, and sex-specific mortality rates, yielding an expected survival probability for each sex. Cumulative incidence curves of

cause-specific mortality were estimated by the cumulative incidence method, taking other causes of deaths as competing risks (23).

Multivariable Poisson regression (21) was used to assess the simultaneous impact of multiple factors on the cause-specific SMRs. Adjustment factors included sex, age at diagnosis, year of diagnosis, and years since diagnosis (all categorical variables). Using the logarithm of expected numbers of deaths based on US mortality rates as offsets, we assessed the influence of radiotherapy exposure and dose levels of alkylating agents, anthracyclines, epipodophyllotoxins, and bleomycin, controlling for the adjustment variables above. The same model was fitted to each cause-specific SMR, namely, subsequent cancer mortality, cardiac-related mortality, pulmonary-related mortality, external-cause mortality, and all-other-cause mortality. We also a priori hypothesized interactions of specific treatment exposures for each cause-specific SMR: radiation and alkylating agents, radiation and anthracyclines, radiation and epipodophyllotoxin, and radiation and bleomycin. In each Poisson regression model, we tested the equality of its dispersion parameter to unity; none of our models had evidence for overdispersion.

Absolute excess risk was calculated as an additional metric of the impact of treatment on cause-specific mortality in the CCSS cohort. Absolute excess risk was determined for each cause-specific category by subtracting the expected number of deaths (calculated from the US population) from the observed number of deaths in the cohort, dividing the difference by the person-years of follow-up, and multiplying by one thousand.

Multiple imputations, under the assumption of "missing at random" (24), were applied for missing data on survivors whose medical records information was not available due to refusal, loss to follow-up, or delay in submitting the medical record release form. For each survivor with one or more missing values of medical record variables (there were 7894 survivors with all medical record variables missing and an additional 1334 survivors with some values missing), we identified a group of survivors who

Table 1. Life status and standardized mortality ratios in 5-year survivors of the childhood cancer in the Childhood Cancer Survivor Study*

Patient set	Eligible cohort, No. of patients	Alive, No. of patients	Dead, No. of patients	SMR†	95% CI	*P* value
All patients	20483	17662	2821	8.4	8.0 to 8.7	
Sex						<.001
Male	11322	9636	1686	6.7	6.4 to 7.0	
Female	9161	8026	1135	13.2	12.5 to 14.0	
Age at diagnosis, y						<.001
0–4	8181	7361	820	9.1	8.5 to 9.8	
5–9	4600	3984	616	8.4	7.7 to 9.1	
10–14	4142	3475	667	7.9	7.3 to 8.5	
15–20	3560	2842	718	7.9	7.4 to 8.5	
Year of diagnosis						<.001
1970–1973	2931	2267	664	8.2	7.6 to 8.9	
1974–1977	4297	3562	735	8.0	7.4 to 8.6	
1978–1981	5364	4693	671	7.9	7.3 to 8.5	
1982–1986	7891	7140	751	11.1	10.4 to 12.0	
Survival after diagnosis, y						<.001
5–9	—	—	1336	20.7	19.6 to 21.8	
10–14	—	—	611	7.2	6.6 to 7.7	
15–19	—	—	431	4.7	4.2 to 5.1	
20–24	—	—	268	4.3	3.8 to 4.9	
25–29	—	—	144	5.0	4.2 to 5.9	
30–34	—	—	31	6.9	4.7 to 9.8	
Diagnosis						<.001
Leukemia	6395	5482	913	10.0	9.4 to 10.7	
Acute lymphoblastic leukemia	5760	5030	730	9.5	8.8 to 10.2	
Acute myeloid leukemia	501	421	80	11.5	9.1 to 14.3	
Other leukemia	494	391	103	14.7	12.0 to 17.8	
CNS tumors	2821	2275	546	12.9	11.8 to 14.0	
Astrocytomas	1807	1489	318	11.3	10.1 to 12.6	
Medulloblastoma, PNET	552	424	128	17.7	14.8 to 21.1	
Other CNS malignancy	462	362	100	14.1	11.5 to 17.1	
Hodgkin disease	2717	2207	510	7.8	7.1 to 8.5	
Non-Hodgkin lymphoma	1524	1381	143	4.4	3.7 to 5.2	
Kidney tumors	1735	1638	97	4.6	3.8 to 5.6	
Neuroblastoma	1358	1274	84	5.6	4.4 to 6.9	
Soft tissue sarcoma	1838	1594	244	7.1	6.2 to 8.1	
Bone tumors	1735	1451	284	7.8	7.0 to 8.8	
Ewing sarcoma	568	432	136	13.3	11.2 to 15.8	
Osteosarcoma	1068	930	138	5.9	4.9 to 6.9	
Other bone tumors	99	89	10	4.1	2.0 to 7.5	

* As of December 30, 2002. SMR = standardized mortality ratio; CI = confidence interval; CNS = central nervous system; PNET = primitive neuroectodermal tumor.

† All SMRs were age and sex standardized according to the US mortality rates from the National Center for Health Statistics.

matched on the following four variables and replaced the missing values with the values of a randomly sampled survivor in the group. The four matching variables were: original cancer, age at diagnosis (5-year age groups); calendar year of diagnosis (4-year calendar periods); the institution that treated the original cancer; and the vital status. This imputation was repeated 10 times, creating 10 complete datasets without missing values. The analysis of treatment-factor effects, which was the only analysis that used the multiple-imputation data, was conducted 10 times using the 10 datasets, and the results were summarized by the standard method for combining multiple-imputation analyses (25). By repeating the imputation and analysis 10 times, we represented uncertainties of missing values in between-imputation variability.

Results

Overall Mortality

Among this cohort of 20483 eligible 5-year survivors, a total of 2821 deaths (13.8%) were ascertained (Table 1). Survivors had 8.4 times higher mortality following their 5-year survival after diagnosis compared with the age-, sex-, and year-matched US population (95% confidence interval [CI] = 8.0 to 8.7; $P < .001$). The SMR was higher for females (SMR = 13.2, 95% CI = 12.5 to 14.0) than males (SMR = 6.7, 95% CI = 6.4 to 7.0) ($P < .001$). Figure 1 describes the survival of 5-year survivors by sex, in comparison with the age-, sex-, and year-matched US mortality rates. Overall survival probabilities were estimated to be 93.5% (95% CI = 93.1 to 93.8) at 10 years, 88.1% (95% CI = 87.6 to 88.5) at 20 years, and 81.9% (95% CI = 81.1 to 82.7) at 30 years. All-cause 30-year cumulative mortality was 18.1% (95% CI = 17.3 to 18.9) for 5-year survivors, 12.4% (95% CI = 11.6 to 10.3) for 10-year survivors, 9.5% (95% CI = 8.7 to 10.3) for 15-year survivors, and 7.0% (95% CI = 6.3 to 7.8) for 20-year survivors (Figure 2).

Survivors diagnosed before 4 years of age had a somewhat higher risk of late mortality (Table 1). Highest SMRs were observed among 5-year survivors of other leukemia (non–acute lymphoblastic leukemia [ALL], non–acute myeloid leukemia [AML]), medulloblastoma or primitive neuroectodermal tumor (PNET), other CNS malignancy (non-astrocytoma), and Ewing sarcoma. The highest mortality rate was observed within the first 5 years of entering the cohort (ie, 5–9 years after diagnosis), when the risk of death due to recurrence and/or progressive disease would be expected to be the greatest. Individuals treated in the most recent years (1982–1986) also showed the highest SMR, when compared with those treated in earlier years. However, after adjustment for time since diagnosis, the mortality rate was slightly elevated in earlier treatment years and was decreased in more recent diagnosis cohorts (relative rates [RRs] relative to 1982–1986 diagnosis: 1970–1973, RR = 1.3 [95% CI = 1.2 to 1.5], $P < .001$; 1974–1977, RR = 1.2 [95% CI = 1.1 to 1.3], $P < .001$; and 1978–1981, RR = 1.0 [95% CI = 0.9 to 1.1], $P = .54$).

Cause-Specific Mortality

Recurrence and/or progressive disease accounted for the majority of deaths (57.5%), with subsequent neoplasms, diseases of the circulatory system, and diseases of the respiratory system accounting for 18.6%, 6.9%, and 2.6% of deaths, respectively (Table 2). Females had a higher proportion of deaths attributed to subsequent malignancy; males had a higher proportion of deaths due to cardiac outcomes.

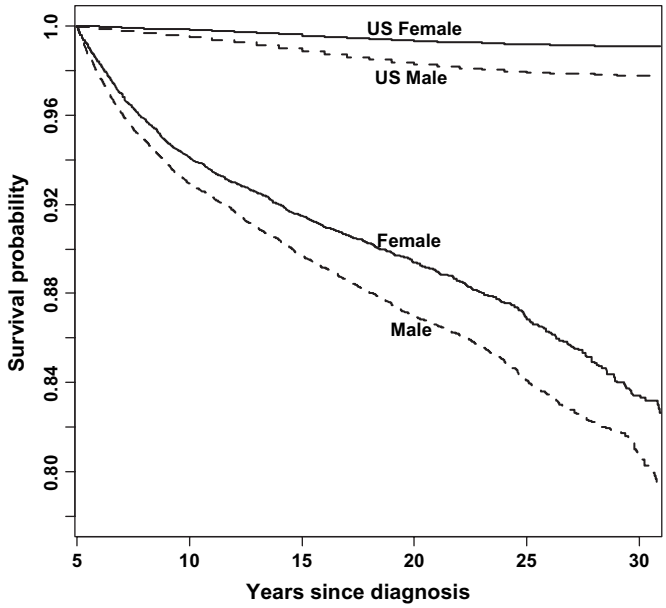

Figure 1. Overall survival according to sex in the Childhood Cancer Survivor Study cohort and expected survival based on age-, year-, and sex-matched US population mortality rates.

The cumulative proportion of deaths due to recurrence or progression was approximately 6.3% (95% CI = 5.9 to 6.6) at 15 years after diagnosis, and it increased to 7.8% (95% CI = 7.3 to 8.2) at 30 years after diagnosis (Figure 3). Cumulative mortality from a subsequent new malignancy increased fairly constantly starting at entry into the cohort to a 30-year mortality of 3.5% (95% CI = 2.9% to 4.2%). Deaths from pulmonary, cardiac, and other causes were relatively low during the 5- to 15-year interval, but increases were observed 15–30 years after diagnosis of the original cancer.

Overall survival differed appreciably according to the original diagnosis. We observed low all-cause cumulative mortality rates in survivors of kidney tumors and neuroblastoma (data not shown), and the nonrecurrence and nonexternal cause cumulative mortality rates were high for individuals diagnosed with Hodgkin disease and Ewing sarcoma.

The overall rate of mortality as a result of recurrence or progressive disease in this cohort was 0.44% per year (95% CI = 0.41 to 0.46) (Table 3). A statistically significant difference in the rate of mortality due to recurrence or progression was seen by sex, age at diagnosis, years since diagnosis, and diagnosis. As anticipated, the rate of death due to recurrence or progression was highest in the 5- to 10-year period after diagnosis, at 0.99% per year (95% CI = 0.93 to 1.06), and this rate decreased dramatically to 0.10% per year (95% CI = 0.06 to 0.16) in the period 25–29 years after diagnosis. At 30–34 years after diagnosis, recurrence was the smallest contributor to mortality. Rates of deaths for other causes increased from time of diagnosis. Starting at 20–24 years of follow-up, the death rate due to second malignancy exceeded the death rate from recurrence.

Females had higher SMRs than males in each cause-specific category except for deaths due to external causes (Table 4). Rates

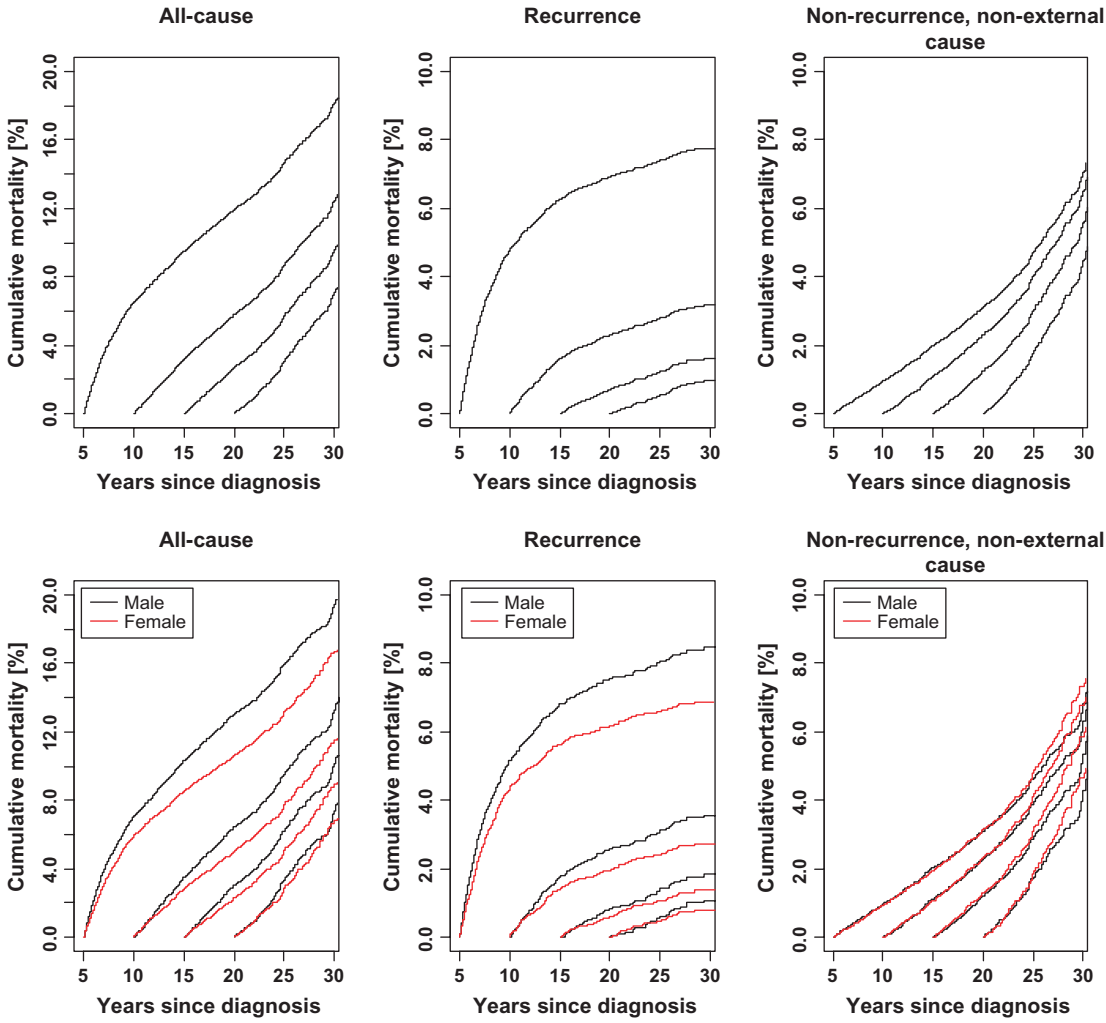

Figure 2. Overall conditional cumulative mortality curves, conditioned on survival of 5, 10, 15, and 20 years since the original diagnosis. Separate curves were generated for deaths due to any cause, those due to recurrence, and those not due to recurrence or external causes (defined in "Methods").

of death due to subsequent new malignancies were statistically significantly elevated in all diagnostic groups relative to the general population. Rates were not statistically significantly elevated for deaths due to all external causes; rates were also not elevated for specific external causes, such as motor vehicle accidents (SMR = 1.0, 95% CI = 0.8 to 1.3), other accidents (SMR = 1.3, 95% CI = 1.0 to 1.8), or suicide (SMR = 1.0, 95% CI = 0.7 to 1.4) (in table).

To investigate independent risk factors of late mortality, multivariable Poisson regression analyses of cause-specific SMRs were performed for causes of deaths not due to recurrence (Table 5). Several independent risk factors for death from a subsequent new malignancy, including female sex, exposure to radiation therapy, high exposure to alkylating agents, and the inclusion in the top tertile for epipodophyllotoxin exposure, mirrored those associated with the risk of developing a subsequent new malignancy (3). Age less than 5 years at initial cancer diagnosis and follow-up of less than 20 years were also associated with a higher rate of death due to subsequent new malignancy. Statistically significant risk factors for death due to cardiac causes were the same as those found in studies of the cardiotoxic effects of treatment, including cardiac radiation and cumulative exposure to anthracyclines (26). Female sex, age 5–9 years at cancer diagnosis, follow-up of 5–9 years from diagnosis, and exposure to radiation therapy were associated with a statistically significant increase in SMRs for other causes of death (ie, those not due to recurrence, external causes, new malignancy, or cardiac or pulmonary disease). Epipodophyllotoxin exposure was associated with an increased SMR for pulmonary-related mortality. Tests for interaction between specific treatment exposures—radiation and alkylating agents, radiation and anthracyclines, radiation and epipodophyllotoxin, and radiation and bleomycin—did not attain statistical significance.

Absolute Excess Risk

In the CCSS cohort, the absolute excess risk of all-cause mortality among 5-year survivors of childhood cancer was 7.36 deaths per 1000 person-years. Excluding recurrences, the absolute excess risk of death due to subsequent new malignancy, cardiac causes, and pulmonary causes was 1.30, 0.36, and 0.18 deaths per 1000 person-years, respectively. Additional absolute excess risk estimates are available in Appendix 2.

Table 2. Frequency of deaths by different causes in the Childhood Cancer Survivor Study

Specific cause of death	Total	Males	Females
Recurrence/progressive disease	1469	882	587
Other medical causes of death (ICD codes)	879	477	402
Infectious and parasitic diseases (001–139)	48	23	25
Subsequent neoplasm (140–239)	470	242	228
Lip, oral cavity, and pharynx (140–149)	7	4	3
Digestive organs and peritoneum (150–159)	38	16	22
Respiratory and intrathoracic organs (160–165)	23	10	13
Bone, connective tissue, and skin (170–173)	86	47	39
Breast (174–175)	38	0	38
Genitourinary organs (179–189)	23	8	15
Brain and nervous system (191–192)	73	52	21
Lymphatic and hematopoietic (200–208)	129	75	54
Other subsequent cancer	53	30	23
Endocrine, nutritional, and metabolic diseases and immunity disorders (240–279)	14	7	7
Disease of blood and blood-forming organs (280–289)	9	5	4
Mental disorders (290–319)	7	5	2
Diseases of the nervous system and sense organs (320–389)	21	9	12
Diseases of the circulatory system (390–459)	176	110	66
Ischemic heart disease (410–414)	44	32	12
Cardiomyopathy (425)	46	28	18
Heart failure (428)	6	4	2
Cerebrovascular diseases (430–438)	19	11	8
Other cardiac conditions	61	35	26
Diseases of the respiratory system (460–519)	67	39	28
Pneumonia (480–486)	24	14	10
Pulmonary fibrosis (515)	13	8	5
Other pulmonary causes	30	17	13
Diseases of the digestive system (520–579)	28	15	13
Diseases of the genitourinary system (580–629)	8	5	3
Complications of the puerperium (670–676)	1	0	1
Diseases of the musculoskeletal system and connective tissue (710–739)	8	3	5
Congenital anomalies (740–759)	8	4	4
Symptoms, signs, and ill-defined conditions (780–799)	14	10	4
External causes of injury and poisoning (E800–E999)	186	152	34
Motor vehicle accidents (E810–E825)	80	67	13
Other accidents (E826–E929)	44	37	7
Suicide (E950–E959)	39	35	4
Homicide (E960–E978)	17	10	7
Other injury (E980–E999)	6	3	3
Unknown cause of death	287	175	112

ICD = International Classification of Diseases.

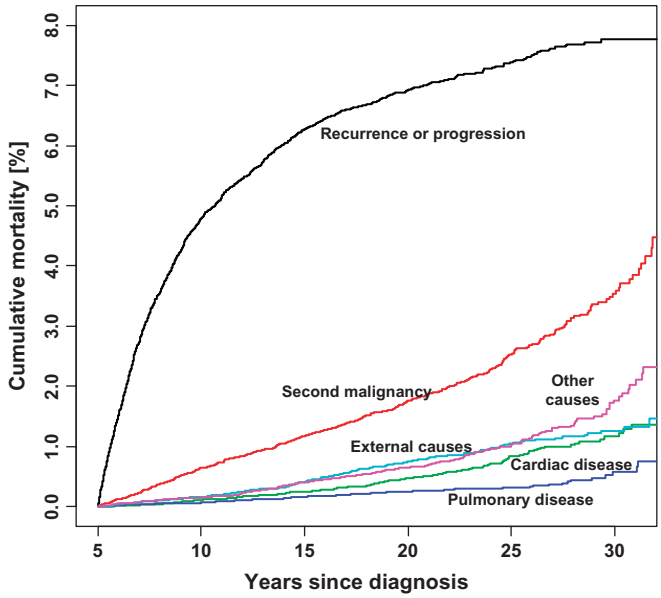

Figure 3. Cumulative mortality due to recurrence of cancer, second malignancy, cardiac disease, pulmonary disease, external causes, and all other causes.

Discussion

Five-year survival is often heralded as a landmark event for individuals with cancer, and it is a good indicator of success in the therapy of the original disease. Unfortunately, 5-year survivors may continue to face elevated morbidity and mortality risks as a result of the original cancer and related therapy. The CCSS is the largest cohort of long-term survivors of childhood and adolescent cancer that has been studied, and between 16 and 32 years of follow-up dating from the cancer diagnosis has been achieved for each survivor. The overall SMR for this cohort has decreased from 10.8 in the last report (13), which covered 10–26 years of follow-up, to 8.4 in this report. This decrease in SMR does not necessarily mean that the mortality rate has declined: As the cohort ages, the expected number of deaths based on the US general population, the denominator of the SMR, increases. The overall absolute excess risk of mortality for this cohort is 7.36, representing an additional seven deaths per 1000 individuals who have been followed for 1 year. We also found a change in the proportion of cause-specific deaths since the last report, with the proportion of deaths due to recurrence decreasing and the treatment-related deaths increasing.

With the benefit of increased follow-up, we were able to conduct a number of death-specific analyses that were not possible in our previous analysis. In that analysis, individuals diagnosed with leukemia, CNS tumors, and bone tumors had the highest overall SMRs (13). In the current analysis, we observed that survivors within specific diagnostic groups of medulloblastoma or PNET, Ewing sarcoma, and leukemias other than ALL and AML had the highest SMRs. We demonstrated that the relative rate of mortality after surviving 15 years after diagnosis decreases, but continues to remain approximately five times higher than what would be expected based on data from the US general population. The relative contribution of recurrence, late medical effects, and external causes to the mortality rate changes by a statistically significant

Table 3. Yearly mortality rates (%) by cause of death among 5-year survivors of childhood cancer in the Childhood Cancer Survivor Study*

	Recurrence		Subsequent malignancy		Cardiac causes		Pulmonary causes		External causes		Other causes	
Survivor characteristic	**Rate (95% CI)**	***P***	**Rate (95% CI)**	***P***	**Rate (95% CI)**	***P***	**(95% CI)**	***P***	**Rate (95% CI)**	***P***	**Rate (95% CI)**	***P***
Total	0.44 (0.41 to 0.46)		0.14 (0.13 to 0.15)		0.04 (0.04 to 0.05)		0.02 (0.02 to 0.03)		0.06 (0.05 to 0.06)		0.06 (0.05 to 0.07)	
Sex		<.001		.159		.055		.566		<.001		.728
Male	0.48 (0.45 to 0.51)		0.13 (0.12 to 0.15)		0.05 (0.04 to 0.06)		0.02 (0.02 to 0.03)		0.08 (0.07 to 0.10)		0.06 (0.05 to 0.07)	
Female	0.38 (0.35 to 0.42)		0.15 (0.13 to 0.17)		0.03 (0.03 to 0.05)		0.02 (0.01 to 0.03)		0.02 (0.02 to 0.03)		0.06 (0.05 to 0.07)	
Age at diagnosis, y		<.001		<.001		<.001		.025		.001		<.001
0–4	0.33 (0.30 to 0.37)		0.10 (0.08 to 0.12)		0.02 (0.02 to 0.03)		0.01 (0.01 to 0.02)		0.04 (0.03 to 0.05)		0.03 (0.02 to 0.04)	
5–9	0.44 (0.40 to 0.49)		0.11 (0.08 to 0.13)		0.03 (0.02 to 0.05)		0.01 (0.01 to 0.02)		0.06 (0.05 to 0.08)		0.06 (0.05 to 0.08)	
10–14	0.50 (0.45 to 0.56)		0.15 (0.13 to 0.19)		0.04 (0.03 to 0.06)		0.03 (0.02 to 0.04)		0.08 (0.06 to 0.11)		0.08 (0.06 to 0.11)	
15–20	0.59 (0.53 to 0.66)		0.27 (0.23 to 0.31)		0.10 (0.08 to 0.13)		0.03 (0.02 to 0.05)		0.06 (0.04 to 0.08)		0.10 (0.08 to 0.13)	
Year of diagnosis		.137		<.001		<.001		<.001		.018		.027
1970–1973	0.48 (0.43 to 0.54)		0.20 (0.17 to 0.24)		0.05 (0.04 to 0.07)		0.04 (0.02 to 0.06)		0.04 (0.02 to 0.06)		0.08 (0.06 to 0.11)	
1974–1977	0.43 (0.38 to 0.47)		0.16 (0.13 to 0.19)		0.06 (0.05 to 0.08)		0.02 (0.01 to 0.04)		0.06 (0.05 to 0.08)		0.06 (0.05 to 0.08)	
1978–1981	0.40 (0.36 to 0.45)		0.11 (0.09 to 0.13)		0.04 (0.03 to 0.06)		0.01 (0.00 to 0.02)		0.07 (0.05 to 0.09)		0.05 (0.03 to 0.06)	
1982–1986	0.44 (0.40 to 0.48)		0.11 (0.09 to 0.13)		0.02 (0.01 to 0.03)		0.02 (0.01 to 0.02)		0.05 (0.03 to 0.06)		0.05 (0.04 to 0.07)	
Survival after diagnosis, y		<.001		<.001		<.001		<.001		<.001		<.001
5–9	0.99 (0.93 to 1.06)		0.13 (0.11 to 0.16)		0.02 (0.01 to 0.03)		0.01 (0.01 to 0.02)		0.03 (0.02 to 0.05)		0.03 (0.02 to 0.04)	
10–14	0.33 (0.29 to 0.37)		0.12 (0.10 to 0.14)		0.03 (0.02 to 0.04)		0.02 (0.01 to 0.03)		0.05 (0.04 to 0.07)		0.06 (0.04 to 0.07)	
15–19	0.15 (0.12 to 0.18)		0.13 (0.10 to 0.15)		0.05 (0.04 to 0.07)		0.02 (0.01 to 0.03)		0.08 (0.06 to 0.10)		0.05 (0.04 to 0.07)	
20–24	0.11 (0.08 to 0.14)		0.17 (0.13 to 0.21)		0.08 (0.05 to 0.11)		0.02 (0.01 to 0.03)		0.06 (0.04 to 0.09)		0.08 (0.06 to 0.12)	
25–29	0.10 (0.06 to 0.16)		0.23 (0.17 to 0.31)		0.08 (0.05 to 0.14)		0.05 (0.02 to 0.09)		0.05 (0.02 to 0.09)		0.16 (0.11 to 0.23)	
30–34	0.05 (0.00 to 0.26)		0.46 (0.22 to 0.84)		0.14 (0.03 to 0.40)		0.09 (0.01 to 0.33)		0.09 (0.01 to 0.33)		0.32 (0.13 to 0.66)	
Diagnosis		<.001		<.001		<.001		<.001		.035		<.001
Acute lymphoblastic leukemia	0.53 (0.48 to 0.58)		0.10 (0.08 to 0.12)		0.02 (0.01 to 0.03)		0.01 (0.00 to 0.02)		0.04 (0.03 to 0.05)		0.04 (0.03 to 0.06)	
Acute myeloid leukemia	0.55 (0.40 to 0.74)		0.09 (0.04 to 0.19)		0.03 (0.00 to 0.09)		0.05 (0.01 to 0.13)		0.10 (0.04 to 0.21)		0.07 (0.02 to 0.15)	
Other leukemia	0.89 (0.69 to 1.13)		0.14 (0.07 to 0.26)		0.03 (0.00 to 0.09)		0.07 (0.02 to 0.15)		0.03 (0.00 to 0.09)		0.01 (0.00 to 0.07)	
Astrocytomas	0.63 (0.54 to 0.73)		0.11 (0.07 to 0.15)		0.03 (0.02 to 0.06)		0.05 (0.02 to 0.08)		0.07 (0.04 to 0.10)		0.09 (0.06 to 0.13)	
Medulloblastoma, PNET	1.14 (0.92 to 1.40)		0.16 (0.09 to 0.28)		—		0.01 (0.00 to 0.07)		0.04 (0.01 to 0.11)		0.04 (0.01 to 0.11)	
Other CNS tumors	0.95 (0.73 to 1.21)		0.10 (0.04 to 0.21)		—		0.03 (0.00 to 0.11)		0.13 (0.06 to 0.25)		0.12 (0.05 to 0.23)	
Hodgkin disease	0.33 (0.28 to 0.38)		0.32 (0.27 to 0.37)		0.79 (0.60 to 1.01)		0.04 (0.02 to 0.06)		0.07 (0.05 to 0.10)		0.10 (0.07 to 0.13)	
Non-Hodgkin lymphoma	0.15 (0.10 to 0.20)		0.14 (0.10 to 0.20)		0.19 (0.10 to 0.33)		0.02 (0.01 to 0.05)		0.07 (0.04 to 0.12)		0.06 (0.03 to 0.10)	
Kidney tumors	0.07 (0.05 to 0.11)		0.09 (0.06 to 0.13)		0.02 (0.01 to 0.04)		0.01 (0.00 to 0.02)		0.04 (0.02 to 0.06)		0.04 (0.02 to 0.07)	
Neuroblastoma	0.18 (0.13 to 0.24)		0.05 (0.03 to 0.09)		0.01 (0.00 to 0.03)		0.02 (0.00 to 0.04)		0.05 (0.02 to 0.08)		0.03 (0.01 to 0.05)	
Soft tissue sarcoma	0.38 (0.31 to 0.45)		0.14 (0.11 to 0.19)		0.03 (0.01 to 0.06)		0.01 (0.00 to 0.03)		0.05 (0.03 to 0.08)		0.07 (0.05 to 0.11)	
Ewing sarcoma	0.95 (0.76 to 1.18)		0.22 (0.13 to 0.34)		0.03 (0.01 to 0.07)		0.01 (0.00 to 0.06)		0.06 (0.02 to 0.14)		0.12 (0.06 to 0.21)	
Osteosarcoma	0.42 (0.33 to 0.53)		0.11 (0.07 to 0.17)		0.02 (0.01 to 0.05)		0.01 (0.00 to 0.04)		0.08 (0.04 to 0.13)		0.05 (0.02 to 0.10)	
Other bone tumors	0.41 (0.17 to 0.85)		0.06 (0.00 to 0.33)		—		—		0.06 (0.00 to 0.33)		—	

* "Subsequent malignancy" refers to a new neoplasm. "Other causes" includes deaths not due to recurrence; subsequent malignancy; or cardiac, pulmonary, or external causes. "External causes" include nonmedical deaths (ie, accidents, homicides, and suicides). CI = confidence interval; PNET = primitive neuroectodermal tumor; CNS = central nervous system.

Table 4. Cause-specific standardized mortality ratios and 95% confidence intervals, excluding deaths due to recurrence*

Patient characteristic or diagnosis	Subsequent malignancy		Cardiac causes		Pulmonary causes		Other causes		External causes	
	SMR (deaths) (95% CI)	*P*†	SMR (deaths) (95% CI)	*P*†	SMR (deaths) (95% CI)	*P*†	SMR (deaths) (95% CI)	*P*†	SMR (deaths) (95% CI)	*P*†
All cases	15.2 (470) (13.9 to 16.6)		7.0 (142) (5.9 to 8.2)		8.8 (67) (6.8 to 11.2)		2.6 (200) (2.3 to 3.0)		0.9 (186) (0.8 to 1.1)	
Sex		.108		.044		.776		<.001		.812
Male	14.2 (242) (12.4 to 16.1)		6.2 (89) (5.0 to 7.6)		8.5 (39) (6.1 to 11.7)		2.1 (107) (1.7 to 2.5)		0.9 (152) (0.8 to 1.1)	
Female	16.4 (228) (14.4 to 18.7)		8.9 (53) (6.6 to 11.6)		9.2 (28) (6.1 to 13.2)		3.8 (93) (3.1 to 4.7)		0.9 (34) (0.6 to 1.2)	
Diagnosis		.001		<.001		.004		.069		.289
Acute lymphoblastic leukemia	14.7 (89) (11.8 to 18.1)		4.2 (15) (2.3 to 6.9)		4.2 (7) (1.7 to 8.6)		2.5 (37) (1.8 to 3.4)		0.7 (35) (0.5 to 1.0)	
Acute myeloid leukemia	11.1 (7) (4.4 to 22.9)		5.0 (2) (0.6 to 18.1)		24.9 (4) (6.7 to 63.8)		3.2 (5) (1.0 to 7.4)		1.9 (8) (0.8 to 3.8)	
Other leukemia	19.0 (11) (9.5 to 33.9)		5.4 (2) (0.6 to 19.4)		32.6 (5) (10.5 to 76.1)		0.7 (1) (0.0 to 3.8)		0.4 (2) (0.1 to 1.6)	
Astrocytomas	12.4 (31) (8.4 to 17.6)		6.2 (10) (3.0 to 11.4)		20.7 (13) (11.0 to 35.4)		4.0 (25) (2.6 to 6.0)		1.1 (19) (0.7 to 1.7)	
Medulloblastoma, PNET	23.4 (13) (12.4 to 40.0)		0.0 (0) (0.0 to 10.8)		6.6 (1) (0.1 to 36.7)		2.1 (3) (0.4 to 6.2)		0.6 (3) (0.1 to 1.9)	
Other CNS tumors	11.4 (7) (4.6 to 23.5)		0.0 (0) (0.0 to 8.6)		12.8 (2) (1.4 to 46.3)		4.9 (8) (2.1 to 9.7		2.1 (9) (1.0 to 4.0)	
Hodgkin disease	20.0 (149) (16.9 to 23.5)		11.9 (62) (9.1 to 15.3)		10.8 (17) (6.3 to 17.2)		2.6 (46) (1.9 to 3.5)		1.0 (33) (0.7 to 1.4)	
Non-Hodgkin lymphoma	14.0 (37) (9.8 to 19.3)		6.5 (13) (3.5 to 11.1)		9.1 (6) (3.3 to 19.7)		2.1 (15) (1.2 to 3.4)		1.0 (19) (0.6 to 1.5)	
Kidney tumors	16.4 (27) (10.8 to 23.8)		12.7 (11) (6.3 to 22.8)		4.2 (2) (0.5 to 15.1)		3.1 (12) (1.6 to 5.5)		0.8 (11) (0.4 to 1.4)	
Neuroblastoma	10.9 (13) (5.8 to 18.7)		5.0 (3) (1.0 to 14.6)		11.4 (4) (3.1 to 29.3)		2.2 (6) (0.8 to 4.8)		1.1 (11) (0.5 to 1.9)	
Soft tissue sarcoma	13.8 (46) (10.1 to 18.4)		4.0 (9) (1.8 to 7.6)		3.8 (3) (0.8 to 11.1)		2.8 (23) (1.8 to 4.2)		0.8 (16) (0.5 to 1.3)	
Ewing sarcoma	20.0 (19) (12.0 to 31.3)		12.0 (8) (5.2 to 23.6)		4.4 (1) (0.1 to 24.3)		4.0 (10) (1.9 to 7.3)		0.9 (5) (0.3 to 2.0)	
Osteosarcoma	8.1 (20) (4.9 to 12.4)		3.9 (7) (1.6 to 8.1)		3.6 (2) (0.4 to 12.9)		1.4 (9) (0.6 to 2.7)		1.1 (14) (0.6 to 1.9)	
Other bone tumors	3.4 (1) (0.0 to 18.9)		0.0 (0) (0.0 to 16.8)		0.0 (0) (0.0 to 60.0)		0.0 (0) (0.0 to 5.3)		0.9 (1) (0.0 to 4.8)	
Years since original diagnosis‡		<.001		.002		.200		.034		.418
5–9	26.8 (131) (22.4 to 31.8)		10.9 (22) (6.9 to 16.6)		9.9 (14) (5.4 to 16.5)		2.9 (30) (1.9 to 4.1)		0.7 (34) (0.5 to 1.0)	
10–14	18.5 (110) (15.2 to 22.2)		8.2 (28) (5.5 to 11.9)		11.5 (20) (7.0 to 17.8)		3.3 (53) (2.5 to 4.3)		0.9 (50) (0.6 to 1.1)	
15–19	13.5 (101) (11.0 to 16.4)		7.8 (40) (5.6 to 10.6)		7.7 (15) (4.3 to 12.6)		2.0 (43) (1.4 to 2.7)		1.1 (62) (0.8 to 1.4)	
20–24	10.8 (76) (8.5 to 13.6)		6.4 (34) (4.4 to 8.9)		4.6 (7) (1.9 to 9.5)		2.1 (38) (1.5 to 2.9)		1.0 (29) (0.6 to 1.4)	
≥25	9.4 (52) (7.0 to 12.3)		4.1 (18) (2.4 to 6.4)		11.1 (11) (5.5 to 19.8)		3.4 (36) (2.4 to 4.8)		0.9 (11) (0.5 to 1.6)	

* "Subsequent malignancy" refers to a new neoplasm. "Other causes" includes deaths not due to recurrence; subsequent malignancy; or cardiac, pulmonary, or external causes. "External causes" includes nonmedical deaths (ie, accidents, homicides, and suicides). Cancer deaths resulting from progression of the original cancer are not included in the observed number of events. SMR = standardized mortality ratio; CI = confidence interval; PNET = primitive neuroectodermal tumor; CNS = central nervous system.

† *P* value from test for heterogeneity.

‡ $P < .05$ from test for trend for deaths due to subsequent malignancy and cardiac causes.

Table 5. Relative rate of mortality due to subsequent malignancy, cardiac disease, pulmonary disease, and other causes excluding recurrence and external causes*

	Subsequent malignancy		Cardiac causes		Pulmonary causes		Other causes	
Independent risk factor	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Sex								
Male	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
Female	1.3 (1.1 to 1.5)	.004	1.4 (1.0 to 1.9)	.049	1.1 (0.7 to 1.7)	.719	1.9 (1.5 to 2.4)	<.001
Age at diagnosis, y								
0–4	1.5 (1.1 to 1.9)	.003	2.1 (1.3 to 3.6)	.004	1.6 (0.8 to 3.1)	.215	1.3 (0.9 to 1.9)	.162
5–9	1.1 (0.8 to 1.4)	.722	1.4 (0.9 to 2.3)	.169	1.0 (0.4 to 2.1)	.934	1.5 (1.1 to 2.2)	.020
10–14	0.9 (0.7 to 1.2)	.570	0.8 (0.5 to 1.3)	.441	1.3 (0.7 to 2.5)	.367	1.1 (0.8 to 1.6)	.449
15–20	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
Year of diagnosis								
1970–1973	1.3 (1.0 to 1.8)	.093	1.7 (0.9 to 3.4)	.132	2.3 (1.1 to 4.8)	.035	1.2 (0.7 to 1.8)	.522
1974–1977	1.1 (0.8 to 1.4)	.592	2.1 (1.2 to 3.7)	.013	1.3 (0.6 to 2.8)	.485	0.9 (0.6 to 1.3)	.476
1978–1981	0.8 (0.6 to 1.1)	.168	1.8 (1.0 to 3.1)	.053	0.6 (0.2 to 1.4)	.218	0.8 (0.5 to 1.2)	.269
1982–1986	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
Years since diagnosis								
5–9	2.7 (2.1 to 3.5)	<.001	2.2 (1.3 to 3.6)	.003	1.8 (0.9 to 3.6)	.114	1.6 (1.1 to 2.3)	.021
10–14	1.9 (1.5 to 2.5)	<.001	1.7 (1.0 to 2.7)	.031	2.2 (1.1 to 4.2)	.022	1.4 (1.0 to 2.0)	.080
15–19	1.4 (1.1 to 1.8)	.012	1.5 (1.0 to 2.3)	.045	1.4 (0.7 to 2.8)	.324	0.9 (0.6 to 1.3)	.484
≥20	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
Radiation†								
Yes	2.9 (2.1 to 4.2)	<.001	3.3 (2.0 to 5.5)	<.001	1.4 (0.7 to 2.9)	.320	2.0 (1.3 to 3.1)	<.001
No	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
Alkylating agent score								
Not exposed	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
1–2	1.4 (1.0 to 2.0)	.049	0.6 (0.3 to 1.2)	.170	0.7 (0.3 to 1.7)	.447	1.0 (0.7 to 1.7)	.840
3–4	1.8 (1.1 to 2.8)	.001	0.6 (0.3 to 1.4)	.278	1.2 (0.4 to 3.8)	.770	1.2 (0.8 to 1.9)	.308
≥5	2.2 (1.6 to 3.0)	<.001	1.7 (1.0 to 3.0)	.053	2.0 (0.8 to 4.5)	.116	1.7 (1.0 to 2.9)	.049
Anthracycline								
Not exposed	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
1–100 mg/m^2	1.1 (0.5 to 2.1)	.847	2.5 (0.7 to 9.2)	.155	2.4 (0.7 to 8.7)	.165	1.7 (0.7 to 4.1)	.244
101–250 mg/m^2	1.1 (0.6 to 1.9)	.750	2.3 (0.9 to 6.0)	.093	0.9 (0.2 to 3.6)	.899	1.6 (0.9 to 3.1)	.125
251–400 mg/m^2	1.2 (0.8 to 1.7)	.296	2.2 (1.3 to 4.0)	.006	0.7 (0.2 to 2.4)	.608	1.4 (0.9 to 2.2)	.198
≥401 mg/m^2	1.4 (0.9 to 2.1)	.110	3.1 (1.6 to 5.8*)	<.001	1.9 (0.7 to 5.2)	.208	1.7 (0.9 to 3.0)	.101
Epipodophyllotoxin								
Not exposed	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
1–982 mg/m^2	1.1 (0.4 to 2.7)	.898	0.7 (0.1 to 5.1)	.726	1.4 (0.2 to 11.6)	.783	1.2 (0.3 to 4.5)	.736
983–4108 mg/m^2	1.6 (0.6 to 4.0)	.307	0.8 (0.1 to 6.0)	.818	3.9 (0.8 to 17.9)	.084	0.9 (0.2 to 3.8)	.921
≥4109 mg/m^2	2.3 (1.2 to 4.5)	.013	1.9 (0.4 to 8.5)	.422	–	1.000	0.8 (0.2 to 3.9)	.800
Bleomycin								
Not exposed	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
1–59 mg/m^2	1.2 (0.7 to 2.1)	.581	1.7 (0.8 to 3.9)	.181	0.8 (0.1 to 5.5)	.780	0.8 (0.3 to 2.3)	.715
60–119 mg/m^2	1.2 (0.5 to 2.7)	.686	0.9 (0.3 to 2.8)	.819	0.8 (0.1 to 6.3)	.792	1.0 (0.3 to 3.0)	.951
≥119 mg/m^2	1.9 (0.8 to 4.5)	.164	1.3 (0.3 to 5.7)	.723	2.5 (0.3 to 18.4)	.381	0.6 (0.1 to 3.3)	.550

* "Subsequent malignancy" refers to a new neoplasm. "Other causes" includes deaths not due to recurrence; subsequent malignancy; or cardiac, pulmonary, or external causes. Cancer deaths resulting from progression of the original cancer are not included in the observed number of events. RR = relative rate; CI = confidence interval.

† Radiation is overall radiation for subsequent malignancy; includes chest, spine, or total-body irradiation for mortality due to cardiac causes; includes chest or total-body irradiation for mortality due to pulmonary causes.

extent over time (Table 3). By 20 years of follow-up, the death rate due to second malignancy exceeds the death rate from recurrence. By 30 years, recurrence is the smallest contributor to mortality.

There have been only a limited number of studies evaluating late mortality among childhood cancer survivors (9–16). In all previous studies and the present one, relative mortality rates were highest 5–9 years after diagnosis and then decreased with time. Furthermore, in all studies with information on cause of death, increased mortality rates were found to be due largely to recurrence of the primary disease, with estimates of the proportion of deaths due to recurrence ranging from 61% to 75%, depending on the era of treatment and the distribution of initial cancer diagnoses. In our extended follow-up of childhood cancer survivors, we found that recurrence accounted for 57.5% of deaths.

There were sex-specific differences in frequencies of deaths due to various causes. Males had a higher rate of death due to recurrences, indicating that treatment had not achieved a cure within the first 5 years for some males. Females demonstrated consistently higher SMRs for non–recurrence and non–external related mortality than males. This is consistent with a large body of literature that suggests

that, compared with males, females are at increased risk for numerous adverse long-term outcomes: obesity; poor cardiac outcomes, including the development of congestive heart failure; and other second malignancies, including breast cancer (27). Except for deaths due to subsequent cancers, however, the actual number of deaths was higher in males than in females. SMRs represent multiplicative differences of mortality rates in the cohort of interest relative to a reference population. Therefore, if the reference rates are lower in females, an SMR may be higher in female survivors, even though the actual rate of death in the cohort in females is lower than that in males.

Previous literature has suggested that mortality among 5-year survivors of childhood cancer was higher in earlier treatment eras (pre-1970) than in more recent times (1970 to present), in which multimodal therapy became available (8–10,12). Little information, however, is available on changes in mortality within the modern treatment era. This analysis shows that the rate of death remained rather stable over the treatment era from 1970 to 1986. Furthermore, the rate of death due to recurrence did not change to a statistically significant extent with the year of diagnosis, suggesting that, although 5-year survival has improved, better salvage therapy is needed for patients who are alive and experience recurrence after the 5-year mark. We also found that the adjusted cause-specific SMRs showed slightly decreasing trends over year of diagnosis for subsequent new malignancy and cardiac and pulmonary deaths, indicating possible improvement in modern therapy that would decrease death due to late effects.

When considering the results of this analysis, it is important to note that our ascertainment of the cause of death relied primarily on death certificate information, which previous studies (28,29) have shown to be of imperfect reliability and accuracy, the most common mistakes being failure to list the immediate and underlying cause of death in the correct order on the death certificate. Thus, it must be recognized that some degree of misclassification is inherent in our data. Another limitation of our analysis is the lack of treatment information on a subset of this cohort, for whom we were not able to obtain medical record abstraction permission.

In conclusion, children and adolescents diagnosed with cancer continue to be at elevated risk for death due to recurrence of the primary disease, and as a result of late effects of therapy. Questions that need to be addressed are whether there are other external factors that influence increased mortality rates, for example, the possible effects of early screening for late effects and the importance of genetics in overall survival. Through ongoing surveillance of these survivors, we will be able to clarify the magnitude and components of this elevated risk and ascertain additional emerging patterns of late-occurring mortality.

Appendix 1

The Childhood Cancer Survivor Study (CCSS) is a collaborative, multi-institutional project, funded as a resource by the National Cancer Institute, of individuals who survived 5 or more years after diagnosis of childhood cancer.

CCSS is a retrospectively ascertained cohort of 20 346 childhood cancer survivors diagnosed before age 21 between 1970 and 1986 and approximately 4000 siblings of survivors, who serve as a control group. The cohort was assembled through the efforts of 26 participating clinical research centers in the United States and Canada. The study is currently funded by a U24 resource grant (National Cancer Institute grant No. U24 CA55727) awarded to St Jude Children's Research Hospital. Currently, we are in the process of expanding the cohort to include an additional 14 000 childhood cancer survivors diagnosed before age 21 between 1987 and 1999. For information on how to access and utilize the CCSS resource, visit www.stjude.org/ccss.

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(Appendix continues)

Appendix 1 (Continued).

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Appendix 2. Absolute Excess Risks per 1000 Person-years for Childhood Cancer Survivor Study Cohort, Compared With the US Population

	Subsequent malignancy	Cardiac	Pulmonary	Other causes	External causes
All cases	1.30	0.36	0.18	0.37	0.00
Sex					
Male	1.22	0.40	0.19	0.30	0.00
Female	1.40	0.31	0.16	0.45	0.00
Diagnosis					
Acute lymphoblastic leukemia	0.90	0.12	0.06	0.24	0.00
Acute myeloid leukemia	0.83	0.21	0.50	0.45	0.50
Other leukemia	1.37	0.21	0.64	0.00	0.00
Astrocytomas	0.99	0.29	0.43	0.65	0.06
Medulloblastoma, PNET	1.58	0.00	0.11	0.20	0.00
Other CNS tumors	0.95	0.00	0.27	0.94	0.70
Hodgkin disease	3.01	1.21	0.33	0.61	0.00
Non-Hodgkin lymphoma	1.34	0.43	0.21	0.30	0.00
Kidney tumors	0.83	0.33	0.05	0.27	0.00
Neuroblastoma	0.49	0.10	0.15	0.14	0.03
Soft tissue sarcoma	1.34	0.21	0.07	0.47	0.00
Ewing sarcoma	2.09	0.85	0.09	0.87	0.00
Osteosarcoma	0.99	0.29	0.08	0.15	0.09
Other bone tumors	0.42	0.00	0.00	0.00	0.00
Years since original diagnosis					
5–9	1.28	0.20	0.13	0.36	0.00
10–14	1.11	0.26	0.19	0.46	0.00
15–19	1.18	0.44	0.16	0.36	0.07
20–24	1.53	0.64	0.12	0.54	0.00
≥25	2.29	0.67	0.49	1.26	0.00

CNS = central nervous system; PNET = primitive neuroectodermal tumor.

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